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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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40679	7590	06/16/2005	EXAMINER	
RONALD I. EISENSTEIN NIXON PEABODY LLP 100 summer street BOSTON, MA 02110			DUNSTON, JENNIFER ANN	
			ART UNIT	PAPER NUMBER
			1636	

DATE MAILED: 06/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/269,321	KAELIN JR. ET AL.
	Examiner	Art Unit
	Jennifer Dunston	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 16 December 2004 and 17 March 2005.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 15-27 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 15-27 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on 16 December 2004 is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

- Certified copies of the priority documents have been received.
- Certified copies of the priority documents have been received in Application No. _____.
- Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.

4) Interview Summary (PTO-413)
Paper No(s)/Mail Date _____.

5) Notice of Informal Patent Application (PTO-152)

6) Other: _____.

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DETAILED ACTION

This action is in response to the Amendment, filed 3/17/2005, in which claims 18 and 25 were amended; and claims 28-40 were canceled. Applicants' arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Drawings

The drawings were received on 12/16/2004. These drawings are acceptable.

Claim Rejections - 35 USC § 102

Claims 15 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Weintraub et al (Nature, Vol. 358, pages 259-261, 1992; see the entire reference). **This rejection has been slightly altered to address the amendments to the claims.**

Weintraub et al teach methods of determining whether E2F will function as a positive or negative element within a cell and methods of selectively expressing a gene in a malignant cell as compared to a mitotically active non-malignant cell (e.g. Figure 2; Figure 3; page 260, column 2; page 261, column 1). Weintraub et al use two plasmid nucleic acid cassettes: (i) pTA-ATF-CAT, comprising a constitutive promoter operably linked to the chloramphenicol acetyltransferase (CAT) gene, and (ii) pTA-ATF-E2F-CAT, comprising an E2F responsive promoter operably linked to the CAT gene (e.g. Figure 2). In malignant cells such as the osteosarcoma cell line SAOS-2, the bladder cancer cell line HTB-9 and the cervical carcinoma

cell line C33A, the level of gene expression was greater when the cell was transfected with the pTA-ATF-E2F-CAT plasmid as compared to the pTA-ATF-CAT plasmid (e.g. Figure 2).

Conversely, in the non-malignant cells such as the mink epithelial cell line CCL-64 and the fibroblast cell line of mouse L cells, the level of gene expression was lower when the cell was transfected with the pTA-ATF-E2F-CAT plasmid as compared to the pTA-ATF-CAT plasmid (e.g. Figure 2). Since both sets of experiments use the pTA-ATF CAT plasmid as a reference, it can be concluded that higher levels of expression were observed from the E2F responsive promoter in the malignant cells as compared to the mitotically active non-malignant cells.

Further, Weintraub et al teach that the level of expression from the E2F responsive promoter is greater than the expression of the constitutive promoter in malignant cells as compared to mitotically active non-malignant cells. Next, Weintraub et al transfet the pTA-ATF-E2F-CAT plasmid into C33A cells, wait until the CAT gene is expressed from the E2F responsive promoter and determine the levels of chloramphenicol acetyl transferase present in the cell by quantitating the formation of acetylated chloramphenicol from chloramphenicol and acetyl-CoA (i.e. positive potentiation of cellular products) (e.g. Figure 3; Figure 1 Legend).

Thus, each of the limitations recited by the rejected claims is taught by Weintraub et al.

Claim Rejections - 35 USC § 103

Claims 15, 16, 19-23 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCormick (WO 94/18992, of record; see the entire reference) in view of Weintraub et al (Nature, Vol. 358, pages 259-261, 1992; see the entire reference). **This rejection has been slightly altered to address the amendments to the claims.**

McCormick teaches methods for selectively ablating neoplastic cells or detecting cells lacking p53 and/or RB function by (i) infecting the neoplastic cells with a recombinant virus such as an adenovirus, which is substantially replication deficient in non-neoplastic cells and exhibits at least a partial replication phenotype neoplastic cells, and (ii) expressing a cytotoxic gene, a negative selectable drug gene or a marker gene where expression is correlated with the viral replication phenotype (e.g. Abstract; page 4, lines 23-38; page 5, lines 1-6; page 28, lines 3-10). In one embodiment, a replication deficient adenovirus is administered to a cell population comprising neoplastic cells (e.g. page 6, lines 4-10). The malignant cells described by McCormick include cells such as the osteosarcoma cell line SAOS-2, the osteosarcoma cell line U-2OS, the adenocarcinoma cell line HS700T, and the colon adenocarcinoma cell line DLD-1 (e.g. page 32, lines 5-21). Further, McCormick teaches the administration of the disclosed adenoviral vectors to a tumor mass by direct injection (e.g. page 28, lines 13-19; page 29, line 7). Moreover, the recombinant adenovirus may contain a negative selectable gene such as an HSV tk gene operably linked to an early region enhancer/promoter such as the E2 promoter, so that the negative selectable gene is preferentially transcribed in infected cells which express a replication phenotype (i.e. neoplastic cells) (e.g. page 7, lines 6-15). McCormick teaches the use of the E2 promoter as an especially preferred embodiment, because the E2 promoter contains multiple E2F sites; therefore $RB^{(-)}$ and $p53^{(-)}RB^{(-)}$ cells that lack RB function presumably will exhibit more efficient transcription from the E2 promoter (e.g. page 27, lines 2-22).

McCormick does not teach a method of determining whether the malignant cell expresses sufficient E2F to activate an E2F responsive promoter either to result in increased expression of

a gene operably linked to an E2F responsive promoter when compared to a mitotically active non-malignant cell.

Weintraub et al teach methods of determining whether E2F will function as a positive or negative element within a cell and methods of selectively expressing a gene in a malignant cell as compared to a mitotically active non-malignant cell (e.g. Figure 2; Figure 3; page 260, column 2; page 261, column 1). Weintraub et al use two plasmid nucleic acid cassettes: (i) pTA-ATF-CAT, comprising a constitutive promoter operably linked to the chloramphenicol acetyltransferase (CAT) gene, and (ii) pTA-ATF-E2F-CAT, comprising an E2F responsive promoter operably linked to the CAT gene (e.g. Figure 2). In malignant cells such as the osteosarcoma cell line SAOS-2, the bladder cancer cell line HTB-9 and the cervical carcinoma cell line C33A, the level of gene expression was greater when the cell was transfected with the pTA-ATF-E2F plasmid as compared to the pTA-ATF-CAT plasmid (e.g. Figure 2). Conversely, in the non-malignant cells such as the mink epithelial cell line CCL-64 and the fibroblast cell line of mouse L cells, the level of gene expression was lower when the cell was transfected with the pTA-ATF-E2F plasmid as compared to the pTA-ATF-CAT plasmid (e.g. Figure 2). Since both sets of experiments use the pTA-ATF CAT plasmid as a reference, it can be concluded that higher levels of expression were observed from the E2F responsive promoter in the malignant cells as compared to the mitotically active non-malignant cells.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method taught by Weintraub et al to determine the E2F activity of a malignant cell prior to transforming the cells with recombinant vectors comprising a gene operably linked to an E2 promoter taught by McCormick et al, because the method taught by

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McCormick et al teaches that the E2 promoter contains E2F binding sites and that E2F should be a more efficient transcriptional activator in RB⁽⁻⁾ cells, and Weintraub et al teach a method of determining the level of expression from an E2F responsive promoter in a malignant cell.

One would have been motivated to make such an addition to the methods of McCormick et al, because one would have wanted to confirm what is observed in the malignant cells of McCormick et al is also observed for other types of malignant cells and is dependent upon increased E2F activity. Absent any evidence to the contrary, there would have been a reasonable expectation of success in modifying the teachings of McCormick et al to include the method taught by Weintraub et al.

Claims 15, 16 and 19-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCormick in view of Weintraub et al and Barber et al (US Patent No. 6,310,045, of record; see the entire reference). **This rejection has been slightly altered to address the amendments to the claims.**

The teachings of each of the McCormick and et al references are described above and are applied as before, except:

The McCormick reference teaches a method of transducing neoplastic cells with an adenoviral vector comprising a gene of interest operably linked to an E2 promoter, wherein the gene of interest is a cytotoxin or a suicide gene such as the HSV tk gene. McCormick does not teach a method of determining whether the malignant cell expresses sufficient E2F to activate an E2F responsive promoter either to result in increased expression of a gene operably linked to an E2F responsive promoter when compared to a mitotically active non-malignant cell, or to result

in the expression of higher levels of a gene operably linked to an E2F responsive promoter as compared to expression of the gene operably linked to a constitutive promoter. McCormick does not teach the use of a cytokine, costimulatory molecule or the *Pseudomonas* exotoxin A domain III.

Weintraub et al teach methods of determining whether E2F will function as a positive or negative element within a cell and methods of selectively expressing a gene in a malignant cell as compared to a mitotically active non-malignant cell (e.g. Figure 2; Figure 3; page 260, column 2; page 261, column 1). Weintraub et al use two plasmid nucleic acid cassettes: (i) pTA-ATF-CAT, comprising a constitutive promoter operably linked to the chloramphenicol acetyltransferase (CAT) gene, and (ii) pTA-ATF-E2F-CAT, comprising an E2F responsive promoter operably linked to the CAT gene (e.g. Figure 2). In malignant cells such as the osteosarcoma cell line SAOS-2, the bladder cancer cell line HTB-9 and the cervical carcinoma cell line C33A, the level of gene expression was greater when the cell was transfected with the pTA-ATF-E2F plasmid as compared to the pTA-ATF-CAT plasmid (e.g. Figure 2). Conversely, in the non-malignant cells such as the mink epithelial cell line CCL-64 and the fibroblast cell line of mouse L cells, the level of gene expression was lower when the cell was transfected with the pTA-ATF-E2F plasmid as compared to the pTA-ATF-CAT plasmid (e.g. Figure 2). Since both sets of experiments use the pTA-ATF CAT plasmid as a reference, it can be concluded that higher levels of expression were observed from the E2F responsive promoter in the malignant cells as compared to the mitotically active non-malignant cells.

Barber et al teach the use of viral vector constructs that direct the expression of an immune activator or a tumor proliferation inhibitor in a tumor cell (e.g. Abstract; column 2, lines

40-67; column 10, lines 48-67). Barber et al describe representative examples of immune activators, including modulators such as CD3, ICAM-1 and LFA-1 and lymphokines such as tumor necrosis factor, and interleukins 1 through 11 (e.g. column 6, lines 65-58). Further, Barber et al describe tumor proliferation inhibitors such as the HSV tk gene and *Pseudomonas* exotoxin A domain III (e.g. column 6, lines 59-67; column 7, lines 1-20).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method taught by Weintraub et al to determine the E2F activity of a malignant cell prior to transforming the cells with recombinant vectors comprising a gene operably linked to an E2 promoter taught by McCormick et al, because the method taught by McCormick et al teaches that the E2 promoter contains E2F binding sites and that E2F should be a more efficient transcriptional activator in RB⁽⁻⁾ cells, and Weintraub et al teach a method of determining the level of expression from an E2F responsive promoter in a malignant cell. Further, it would have been obvious to one of ordinary skill in the art to use a gene encoding *Pseudomonas* Exotoxin A domain III taught by Barber et al as the gene operably linked to the E2F responsive promoter, because McCormick teaches the use of a cytotoxin to ablate cancer cells.

One would have been motivated to make such modifications to the methods of McCormick et al, because one would have wanted to confirm what is observed in the malignant cells of McCormick et al is also observed for other types of malignant cells. Further, McCormick teaches the ablation of cancer cells using genes such as a cytotoxin gene but does not describe specific examples. Therefore, one of skill in the art would have been motivated to use either the cytokines, costimulatory molecules or the *Pseudomonas* exotoxin A domain III,

since Barber et al teach the utility of the toxin for the ablation of cancer cells. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 16-18, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCormick in view of Weintraub et al and Raj et al (Oncogene, Vol. 12, pages 1279-1288, 1996; see the entire reference). **This rejection has been slightly altered to address the amendments to the claims.**

The teachings of McCormick are described above and applied as before. Further, McCormick teaches the use of other promoters and/or enhancers (e.g. page 27, lines 2-10).

McCormick does not teach a method of determining whether the malignant cell expresses sufficient E2F to activate an E2F responsive promoter to result in increased expression of a gene operably linked to an E2F responsive promoter when compared to a mitotically active non-malignant cell. McCormick does not teach the various E2F responsive promoters, or that the malignant cell may be a glioma.

Weintraub et al teach methods of determining whether E2F will function as a positive or negative element within a cell and methods of selectively expressing a gene in a malignant cell as compared to a mitotically active non-malignant cell (e.g. Figure 2; Figure 3; page 260, column 2; page 261, column 1). Weintraub et al use two plasmid nucleic acid cassettes: (i) pTA-ATF-CAT, comprising a constitutive promoter operably linked to the chloramphenicol acetyltransferase (CAT) gene, and (ii) pTA-ATF-E2F-CAT, comprising an E2F responsive

promoter operably linked to the CAT gene (e.g. Figure 2). In malignant cells such as the osteosarcoma cell line SAOS-2, the bladder cancer cell line HTB-9 and the cervical carcinoma cell line C33A, the level of gene expression was greater when the cell was transfected with the pTA-ATF-E2F plasmid as compared to the pTA-ATF-CAT plasmid (e.g. Figure 2). Conversely, in the non-malignant cells such as the mink epithelial cell line CCL-64 and the fibroblast cell line of mouse L cells, the level of gene expression was lower when the cell was transfected with the pTA-ATF-E2F plasmid as compared to the pTA-ATF-CAT plasmid (e.g. Figure 2). Since both sets of experiments use the pTA-ATF CAT plasmid as a reference, it can be concluded that higher levels of expression were observed from the E2F responsive promoter in the malignant cells as compared to the mitotically active non-malignant cells.

Raj et al teach the various E2F responsive promoters (e.g. page 1279, column 2). Further, the various promoters directed expression of a reporter gene in the human glioma cell line U-87MG (e.g. Table 2). The expression showed a dose-dependent increase upon addition of the pCMV-E2F expression plasmid to the transfection (e.g. Figure 5B₁).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method taught by Weintraub et al to determine the E2F activity of a malignant cell, and the method taught by Raj et al to determine the E2F activity in a glioma cell prior to transforming the cells with recombinant vectors comprising a gene operably linked to an E2 promoter taught by McCormick et al, because the method taught by McCormick et al teaches that the E2 promoter contains E2F binding sites and that E2F should be a more efficient transcriptional activator in RB⁽⁺⁾ cells, and Weintraub et al teach a method of determining the level of expression from an E2F responsive promoter in a malignant cell. Further, it would have

been obvious to one of ordinary skill in the art to use the various E2F responsive promoters taught by Raj et al, because McCormick teaches the use of an E2F responsive promoter or other various promoters.

One would have been motivated to make such a modifications to the methods of McCormick et al, because one would have wanted to confirm what is observed in the malignant cells of McCormick et al is also observed for other types of malignant cells. Further, McCormick teaches the use of various promoters in the viral expression vector, and one would have been motivated to use the promoters of Raj et al because Raj et al teach varying levels of expression from the E2F responsive promoters. The variable level of promoter activity would allow one skilled in the art to vary the level of a cytotoxin or suicide gene to modulate the cytotoxic effect. Therefore, one of skill in the art would have been motivated to modify the methods of McCormick to include the methods of Weintraub et al and Raj et al and the promoters of Raj et al. Absent any evidence to the contrary, there would have been a reasonable expectation of success in modifying the teachings of McCormick et al to include the methods taught by Weintraub et al and Raj et al and the promoters taught by Raj et al.

Response to Arguments Claim Rejections - 35 USC § 102

Applicant's arguments filed 12/16/2004 have been fully considered but they are not persuasive. The response asserts the following: (i) all Weintraub teaches is that Rb binds to E2F and inhibits its transactivation, (ii) based on the work of Weintraub, one would expect that in any rapidly cycling cells, E2F would activate transcription of E2F promoters, (iii) Weintraub does not teach, suggest or motivate one to look at levels of E2F expression, and (iv) the invention of

the instant specification is not just a higher level of expression that would be expected for an on/off switch, but selective expression of a toxic gene to malignant cells.

The assertion that all Weintraub teaches is that Rb binds to E2F and inhibits its transactivation is not persuasive. Weintraub et al teach each limitation of the rejected claims with regard to the claimed positive action method steps as set forth in the above rejection.

The assertion that the work of Weintraub would lead one to expect that E2F would activate transcription of E2F promoters in any rapidly cycling cells is not persuasive. Weintraub et al teach increased expression of a reporter gene operably linked to an E2F-responsive promoter in malignant cells versus mitotically active non-malignant cells as discussed above and shown in Figure 2 of Weintraub et al.

The assertion that Weintraub does not teach, suggest or motivate one to look at levels of E2F expression is not persuasive. Method step (a) of claim 25 recites, "determining whether the malignant cell expresses sufficient E2F to cause increased expression of a gene operably linked to an E2F responsive promoter when compared to a mitotically active non-malignant cell." Thus, claimed method of looking at levels of E2F expression requires the analysis of gene expression in malignant and mitotically active non-malignant cells using a construct comprising an E2F-responsive promoter operably linked to a gene. As discussed above, Weintraub teaches an E2F-responsiv promoter operably linked to a gene. Weintraub teaches the determination of gene expression in malignant and mitotically active non-malignant cells using this construct. Weintraub teaches an increased level of expression of the gene operably linked to the E2F-responsiv promoter in malignant cells as compared to mitotically active non-malignant cells.

Therefore, Weintraub necessarily teaches the claimed method for looking at levels of E2F expression.

The assertion that the invention of the instant specification is not just a higher level of expression that would be expected for an on/off switch, but selective expression of a toxic gene to malignant cells is not persuasive. The teachings of Weintraub meet each of the limitations of the rejected claims. The teachings of Weintraub and the instant specification are directed to the expression of a gene operably linked to an E2F-responsive promoter in a malignant cell at an increased level when compared to a mitotically active cell (claim 25, method step (a)).

Although Weintraub et al may have hypothesized a different mechanism of action of E2F protein on the E2F-responsive promoter (e.g. off/on trigger), the mechanism by which cellular proteins act upon an E2F-responsive promoter is not a limitation of the claim. The differential action of the proteins in malignant or mitotically active non-malignant cells is an inherent property of those cells. As such, there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference (see MPEP 2112[R-2](II)). Thus, the mechanism of action is inherent property of the Weintraub reference.

Therefore, claims 15 and 25 are anticipated by Weintraub.

Response to Arguments Claim Rejections - 35 USC § 103

Applicant's arguments filed 12/16/2004 have been fully considered but they are not persuasive.

With regard to the combination of the Weintraub and McCormick references, the response asserts the following: (i) the prior art does not teach or suggest a method of using an E2F responsive promoter as claimed to obtain the selective expression demonstrated, (ii) Weintraub provides no motivation for looking at levels of E2F and determining whether they would result in greater expression of a gene operably linked to an E2F responsive promoter than a non-malignant cell, and (iii) the combination of the references would not suggest the claimed invention because there is nothing in any of the references that suggest selective expression.

The assertion that the prior art does not teach or suggest a method of using an E2F responsive promoter as claimed to obtain the selective expression demonstrated is not persuasive. Method step (a) of claim 25 recites, "determining whether the malignant cell expresses sufficient E2F to cause increased expression of a gene operably linked to an E2F responsive promoter when compared to a mitotically active non-malignant cell." Thus, claimed method of looking at levels of E2F expression requires the analysis of gene expression in malignant and mitotically active non-malignant cells using a construct comprising an E2F-responsive promoter operably linked to a gene. As discussed above, Weintraub teaches an E2F-responsive promoter operably linked to a gene. Weintraub teaches the determination of gene expression in malignant and mitotically active non-malignant cells using this construct. Weintraub teaches an increased level of expression of the gene operably linked to the E2F-responsive promoter in malignant cells as compared to mitotically active non-malignant cells. Therefore, Weintraub necessarily teaches the claimed method for looking at levels of E2F expression.

The assertion that Weintraub provides no motivation for looking at levels of E2F and determining whether they would result in greater expression of a gene operably linked to an E2F responsive promoter than a non-malignant cell is not persuasive. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of skill in the art would have been motivated to test the E2F-responsive promoter to determine whether malignant cells have increased expression of a gene operably linked to an E2F-responsive promoter when compared to a mitotically active non-malignant cell because would have wanted to confirm what is observed in the malignant cells of McCormick et al is also observed for other types of malignant cells and is dependent upon increased E2F activity and Weintraub et al teach a method of determining the activity of an E2F-responsve promoter in malignant and non-malignant cells of varying types. As discussed above, McCormick teaches the use of the E2 promoter as an especially preferred embodiment, because the E2 promoter contains multiple E2F sites; therefore RB⁽⁻⁾ and p53⁽⁻⁾RB⁽⁻⁾ cells that lack RB function presumably will exhibit more efficient transcription from the E2 promoter (e.g. page 27, lines 2-22).

The assertion that the combination of the references would not suggest the claimed invention because there is nothing in any of the references that suggest selective expression is not persuasive. The response states that in contrast to Weintraub, "Applicants taught in the

specification and particularly in the Examples that the selectivity achieved and claimed herein is not a result of greater proliferation of malignant cells, but reflects a fundamental difference between a malignant cell and non-malignant cell" (page 15, 1st full paragraph). As stated in the response, the selective expression from an E2F-responsive promoter is an inherent property of malignant cells. As such, there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference (see MPEP 2112[R-2](II)). Thus, by introducing an E2F-responsive promoter into a malignant cell as taught by Weintraub and McCormick, selective expression would occur as it depends upon the proteins and cellular environment of the malignant cells as compared to mitotically active non-malignant cells. The proteins and cellular environment of a malignant cell are inherent properties of the cell and thus are inherently contained in the Weintraub and McCormick references. Thus, by introducing an E2F-responsive promoter, operably linked to a gene, into a malignant cell, Weintraub and McCormick necessarily teach the selective expression of the operably linked gene in the malignant cell.

With regard to the combination of the McCormick, Weintraub and Barber (US Patent No. 6,310,045) references, the response asserts that the Barber reference does not overcome the deficiency in the combination in the combination of the McCormick and Weintraub references in that the Barber reference does not suggest the selective expression of gene in malignant cells by first determining whether the malignant cells express sufficient levels of E2F. The response is not persuasive for the reasons set forth above with regard to the combination of the McCormick and Weintraub references. The combination of these references does teach determining whether

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the malignant cells express sufficient levels of E2F and selectively expressing a gene operably linked to an E2F-responsiv promoter in a malignant cell.

With regard to the combination of the McCormick, Weintraub and Raj references, the response asserts that Raj teaches that E2F act in a cell cycle dependent manner and that anti-sense E2F1 showed no significant effect on transcriptional activities of the test promoters. This is not found persuasive because the McCormick and Weintraub references teach the selective expression in malignant cells, and thus the Raj reference is not relied upon for this limitation. Perhaps the inability to affect the transcription from E2F-responsive promoters speaks to the unpredictability of antisense technology. However, as discussed above, Raj teaches a dose-dependent increase in promoter activity upon addition of the pCMV-E2F expression plasmid. Thus, Raj teaches that the promoters are E2F-responsiv.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

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however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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